Remarks

By the foregoing amendment, pending claims 1-37 are cancelled, and new claims 38-53 are submitted; entry of the amended claims and favorable consideration thereof is respectfully requested.

Objections to the Specification

The Examiner has objected to the specification as describing Figure 5 generally instead of providing specific descriptions of both Figures 5a and 5b. By the foregoing amendment the specification has been amended and should resolve the objection. The Examiner has also noted a misspelling of "glycoprotein" which has been corrected. Accordingly, the objections to the drawings and specification should be withdrawn.

Objections to the Claims - §112 Issues

The Examiner has objected to claims 1and 3-5 under 35 U.S.C.§112 on the grounds that "enhancing the level of an immune response" is indefinite. Although those claims are now cancelled, new claims 39, 44, 47 and 49 call for "increasing the levels of B and T cell lymphocyte response" and the following comments are noted.

Physicians and biologists commonly employ the term "increasing" the levels of B and T cells with reference to the levels that would otherwise be present in the absence of the claimed treatment. Since mammals tend to vary in the levels of B and T cells, not only from each other but in each mammal, there is no absolute standard. Thus, the standard is necessarily relative, even for a single mammal, and an increased level is understood to refer to a relative increase in comparison with the "individual" levels present in the absence of the claimed treatment.

The Examiner also objected to use of acronyms in the claims; the amended claims spell out the full name for each element, along with an acronym which is used to

refer to that element in subsequently claim language. In addition, the claims now adopt the Examiner's suggested language for dependent claims, using the clause : "The method according to claim. . ." Therefore, it is respectfully submitted that the rejections under 35 U.S.C. §112 are not applicable to the pending claims.

Objections to the Claims - §102 Issues

The present invention as specified in claims 38-53 relates to a method of treating a mammalian subject to protect against an infectious disease by administration of EtxB to improve the immune response to infectious disease antigens.

Williams, et al (WO 97/02045)

The Examiner has rejected former claim 1 under 35 U.S.C. §102(b) over Williams, et al (WO 97/02045). This rejection is respectfully traversed. Williams relates to therapeutic agents for the treatment of autoimmune diseases, human leukaemia's of T-cell origin, human transplant rejection and graft versus host disease (see page 1, lines 1-9). WO97/02045 does not teach or suggest therapeutic agents for use in the treatment of an infectious disease.

The medical conditions contemplated in WO97/02045 (autoimmune diseases, human T-cell leukaemia's, human transplant rejection and graft versus host disease) are all associated with a pathological immune response. They are all mediated or exacerbated by an inappropriate immune response in the subject. A therapeutic agent for use in the treatment of such conditions would be expected to work by down-regulating the immune response or down-regulating the pathological component of such a response.

Williams is concerned with autoimmune diseases which are exacerbated by an increase in B and T cells, as confirmed by the published study Williams, et al, "Prevention of autoimmune disease due to lymphocyte modulation by the B-subunit of Es-

cherichia coli heat-labile enterotoxin", *Proc. Nat. Acad. Sci. USA*, Vol. 94, pp5290-5295, May 1997 (copy submitted herewith) which describes the research involved in the Williams PCT publication describes the down regulation of B and T cells. At page 5295, left side column, line 20, Williams, et al. report a "decrease" in the "overall magnitude of the in vivo T cell response." Furthermore, the study reports that as a result of the administration of ExtB, "Antigen-presenting cell activation by IFN-r may also be decreased. . ." (*id.*, lines 25-27) The reported conclusion of their study is that, "Indeed, a significant reduction in the severity of experimental autoimmune encephalomyelitis can be achieved after administration of ExtB. . ." Id. at line 51.

In contrast, the claimed method is provides a method to protect against infectious (externally caused) diseases. One skilled in this art would understand that methods employed by Williams to down regulate or decrease the levels of B and T cells to treat autoimmune diseases are the opposite of the desired objective of the claimed method of increasing the levels of B and T cells. One skilled in this art would not arrive at the invention based on the disclosure of Williams. Indeed, the disclosure of Williams teaches away from the claimed method and neither anticipates the claimed invention or makes it obvious. Accordingly, reconsideration and withdrawal of the rejection based on Williams is respectfully requested.

Hazama et al

The Examiner has rejected former claims 1 and 3-5 under 35 U.S.C. §102(b) over Hazama, et al (Immunology 1993). This rejection is respectfully traversed. As explained by the Examiner in paragraph 10 of the Office Action, Hazama et al describes a study of the immune responses elicited by intra-nasal immunization with various forms of a recombinant glycoprotein D (gD) of HSV-1:

1. gD co-administered with LTB (t-gD+LTB);

2. a fusion protein consisting of gD and LTB- t-gD-LTB; and

3. a fusion protein consisting of t-gD and human interleukin 2 (t-gD-IL-2).

The antibody responses elicited by intra-nasal immunization with these antigens are given in Table 1. In this table, the results indicate that a combination of EtxB + t-gD caused the production of a very low level of anti-HSV-1 IgG in the serum (12± mU/ml) and no mucosal anti-HSV on first dose. After a booster immunization the levels of IgG improved (1507±2356) and some IgA was seen in nasal secretions (112±87). The antibody response to the fusion protein (t-gD-LTB) is much greater, both after primary and booster immunization. This fact is recognized by the authors, for example on page 647 where they state: *"Therefore, the fusion protein induced the immune response more efficiently than did co-administration of t-gD and LTB."* (column 1, lines 9-11)

It is clear that the authors do not consider the mucosal immune response generated by the t-gD + LTB mixture to be significant. For example, in the Discussion they state: *"We also demonstrated that t-gD-LTB elicited a mucosal immune response, whereas a mixture in almost the same molecular ratio of t-gD and LTB failed to induce such a response."* (Page 648, col 1, lines 14-17).

In developing the data further they go on to ignore the possible use of the admixture favouring either a fusion protein of EtxB and t-gD or a fusion protein of t-gD and IL-2.

The paper goes on to show the <u>even the fusion protein</u> failed to protect mice from infection with the virus: *". . .although t-gD-LTB elicited a serum IgG response, it failed to protect mice from viral infection."* (page 647, column 2, lines 30-32)

The present invention relates to a method for protecting a subject against an infectious disease. Although Hazama et al show a mixture of EtxB and antigen produces a low-level antibody response, <u>they do not show that this is sufficient to protect against infection</u>.

For disease protection, there must also be a T-cell response. Hazama et al suggest that the mixture of EtxB and antigen does not produce a T-cell response because EtxB may suppress T-cell activity (page 648, column 2, lines 18-24).

Hazama thus does not disclose, much less suggest or teach using a mixture of EtxB and antigen to protect against infection. From the data in Table 1, the skilled person would understand that a fusion protein of EtxB-antigen produces a superior immune response. From the data in Table 4, the skilled person would understand that fusion protein with IL-2, rather than EtxB is capable of protecting mice against viral infection. From the comments in the Discussion section (penultimate paragraph) the skilled person would understand that IL-2 is preferable over EtxB as it does not suppress cytotoxic T lymphocytes.

In contrast, the present invention shows not only a B-cell response but also an increased T-cell response (see Application at p. 39 - Example 11; and Figures 16 and 17). The claimed invention is neither anticipated by nor obvious in view of Hazama

Conclusion

For the reasons stated above, neither Williams nor Hazama et al anticipate or make obvious the claimed method specified in claims 38-53. Accordingly, the Examiner is respectfully requested to withdraw the rejection and allow pending claims 38-53 of the application.

Respectfully submitted,

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